SUMMARY AND DISCUSSION

Clinical observations clearly show the activity of several anticholinergic drugs on some organs in the human body. Atropine has been the prototype of an anticholinergic drug throughout many centuries. Owing to the side effects of atropine on the central nervous system, many investigators have searched for other anticholinergic drugs. As a result from these investigations, tertiary amines and quaternary ammonium compounds were developed with anticholinergic activity after parenteral administration. From the literature review on pharmacokinetics of the anticholinergic drugs, in chapter 2 A, it can be concluded that the results after oral administration of quaternary ammonium compounds are conflicting. Since absorption of quaternary ammonium compounds by means of passive diffusion is difficult, to accept many authors suggested alternative ways of absorption. The results given in the pharmacodynamic review, in chapter 2 B, are also contradictory. In our opinion, it is not clear at this moment whether quaternary ammonium compounds do exert the intended anticholinergic activity in patients after oral and rectal administration and if so, the question arises how this activity on the organs has been obtained? To give an answer to this question we decided to investigate some well-known quaternary ammonium compounds with anticholinergic action, namely butylscopolamine, methylatropine and propantheline. Of the tertiary amines, cetiedil was chosen. Cetiedil is a tertiary ester compound, merely composed of radicals which occur frequently among the anticholinergics; this is discussed in chapter 1, that handled about the structure-activity relationship. In the literature (chapter 2 B) a broad pharmacological activity is claimed for cetiedil, namely both a direct spasmolytic vasodilating effect and anticholinergic properties.

The physicochemical constants of the quaternary ammonium compounds make real absorption unlikely. The pKa values indicate a high pola-

rity and the drugs are therefore fully ionized at any pH, including the "physiological" pH (7.4). Table 19 (chapter 4) demonstrates that high pKa values are correlated with very low distribution coefficients, suggesting poor absorption of these drugs after oral and rectal use. The absorption of the tertiary amine cetiedil should be very good according to the low pKa value of 5.7 and the high distribution coefficient of 0.796. Though atropine is a fairly strong base, (Table 19, chapter 4), it seems to be well absorbed in the human body, possibly due to its good lipid solubility (Mirakhur 1978).

The literature provides only few data on the relationship between dose, plasmalevel, effect and intrinsic potency of the anticholinergic drugs. The present thesis is an evaluation of this relationship. In first instance, the pharmacokinetics of the anticholinergic drugs in man after intravenous, oral and rectal administration were investigated (chapter 4). In second instance, the inhibition of saliva secretion by atropine, as a reference drug, and by the anticholinergics concerned, have been measured, to relate the anticholinergic action to the investigated pharmacokinetic parameters (chapter 5). In third instance, in vitro experiments were performed to investigate the intrinsic potency of the anticholinergic drugs under various experimental conditions (chapter 6).

From chapter 3 it can be concluded that even with sensitive detection methods like spectrophotometry, spectrofluorimetry and gas-liquid chromatography the expectedly very low plasmalevels of the parent quaternary ammonium compounds and their metabolites after oral and rectal drug administration cannot be determined. Therefore it was decided to follow a radiochemical method, which is very sensitive. We have used ^{14}C-labelled compounds. The position of the ^{14}C-atom, the specific activity, the radiochemical purity and the preparation of the parenteral, oral and rectal formulations are reviewed in chapter 3.

The experiments presented in chapter 4 demonstrate that after oral administration of butylscopolamine in 3 subjects, the maximal level of radioactivity in plasma averaged 10 $\pm$ 5 dpm/ml (8 $\pm$ 4 ng/ml); this very low level was reached about 3 hours after drug administration. In 3 other subjects no detectable levels (<4 dpm/ml) were found in plasma between 0-5 hours after oral administration. After oral administration of methylatropine, propantheline and cetiedil the maxi-

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mal level of radioactivity in plasma averaged 12 ± 3 dpm/ml (0.33 ± 0.08 ng/ml), 9 ± 2 dpm/ml (14 ± 3 ng/ml) and 190 ± 20 dpm/ml (3.0 ± 0.3 ng/ml), respectively. These conclusions are supported by the results from chapter 5; in contrast with atropine and cetiedil, i.e. the tertiary compounds, butylscopolamine and methylatropine had no effect on saliva secretion after oral administration, though butylscopolamine was very effective after i.v. injection. Propantheline was effective after oral administration; though this is in accordance with its high pA_2 value, as shown in chapter 6, the dosage of propantheline was also much higher than that of methylatropine.

After rectal administration of the 4 drugs under study no detectable levels were found in plasma. The cumulative excretion of radioactivity in urine within 6 days after oral administration of butylscopolamine, methylatropine, propantheline and cetiedil averaged 1.9%, 14.6%, 10.6% and 77.6% of the administered dose, respectively; after rectal administration percentages of 0.7% (butylscopolamine), 5.3% (methylatropine), 4.0% (propantheline) and 31.6% (cetiedil) were found. The present measurements of radioactivity in human plasma and urine indicate a poor absorption of the quaternary ammonium compounds. As far as the tertiary amine cetiedil is concerned, a very good absorption of labelled compound is obtained.

Since this drug is metabolized very rapidly after intravenous and oral administration, it should be considered as a useless drug, unless active metabolites are formed, and the saliva secretion experiments show that this is what appears to happen. From the saliva secretion experiments can be derived that even 6 hours after the parent drug had disappeared from plasma, an anticholinergic effect was still present. It seems reasonable to assume that this effect must be due to formation of one or more metabolites. Although it should not be concluded that this metabolite is also responsible for the vasodilatory effect of cetiedil observed by Boissier et al. (1974 B), it would seem worthwhile to investigate this with appropriate techniques, once the precise nature of the metabolite(s) has been identified. Simaan and Aviado (1976) presented evidence that in dogs cetiedil appeared to increase femoral blood flow without effecting cardiac muscle, while drugs as papaverine and aminophylline increased femoral blood flow and stimulated the heart. It cannot be concluded from their experiments whether the parent compound or a metabolite is

responsible for the observed effects. However, a long acting compound with the mode of action proposed by these authors and with acceptable anticholinergic side-effects could for instance have a place in bronchodilatation (as mentioned by Cho et al. 1978) and in the treatment of early vascular stenosis, or in spastic conditions of blood vessels. In the first hours after rectal administration of cetiedil, a small amount of drug is present in the general circulation, but after a longer time much more drug has been absorbed. It could be calculated that after rectal administration of cetiedil the urinary radioactivity was approximately 60% of the amount observed after oral administration of cetiedil. This indicates that after rectal administration of cetiedil an anticholinergic action may be present. Another point is that, because of the high concentration gradient over the rectal venes, it remains in that case to be seen whether long-term administration will be harmless in view of the possible vasodilatory effect of cetiedil.

Due to local circumstances it was impossible to compose all individual plasma curves. In general, the intra-individual differences in the plasmalevels were so small that is was justified to present mean plasma curves. The apparent volumes of distribution after intravenous injection of the 4 drugs under study demonstrate a very high value for butylscopolamine (857 l) in relation to methylatropine (55 l), propantheline (30 l) and cetiedil (152 l). The total body clearances of methylatropine, propantheline and cetiedil amounted to 301 ml/min., 372 ml/min. and 383 ml/min., respectively and are exceeding the glomerulus filtration. In the body these drugs are not completely present in unchanged form, as indicated in chapter 4: methylatropine 70% (i.v.) and 50% (oral); propantheline 40% (i.v.) and 3% (oral); cetiedil 0% (i.v. and oral) in unchanged form. Concerning cetiedil, the total body clearance of 383 ml/min. should be much higher. An explanation for a higher clearance may be that 5 minutes after i.v. injection only 50% of the present (not cleared) radioactivity is reflecting unchanged drug, and therefore the plasma half-life of pure cetiedil is extremely low (Table 20).

The clearance of butylscopolamine amounted to 714 ml/min. and is high in relation to the other 3 drugs under study. From the experiments in chapter 4 can be derived that butylscopolamine is not metabolized in the human body after intravenous injection. These observations

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indicate that there seems to be an alternative route of elimination for butylscopolamine. There are two suggestions:

1. Since the clearance of butylscopolamine is approximately four times the creatinine clearance and approximates maximal kidney flow (20-25% of the cardiac output, corresponding with 600-750 ml plasma/min.), blood with butylscopolamine that streams through the kidneys should therefore be maximally cleared from drug. This can only by active tubulus secretion; there should be no reabsorption of butylscopolamine. It can be expected that unmetabolized quaternary ammonium compounds, because of their high polarity, enter the glomerulus filtrate by means of active tubulus secretion (Witter et al. 1978).

2. The incomplete cumulative excretion may imply that the excretion of butylscopolamine after 6 days still continues, though (even urine) levels are below the detection limit. Such a very slow excretion phase, together with the very high volume of distribution, should indicate that butylscopolamine accumulates somewhere in the human body. Because of its polarity, it is unlikely that butylscopolamine accumulates mainly in fat, more likely in the wall of the intestines, which suggestion is in accordance with animal studies of Pomeroy and Rand (1968) and Pentikäinen et al. (1973) and studies in man of Vapaatalo et al. (1975) (chapter 2 A). This accumulation could be responsible then for a local antispasmodic action. Of course, different storage sites elsewhere may also be implicated, f.i. acid mucopolysaccharides; this has been shown for bisquaternary ammonium compounds like tubocurarine (Olsen et al. 1975).

Whether the first tentative explanation - i.e. tubular secretion - or the second - i.e. slow releasing storage sites - is valid, requires further examination. Respectively, studies with competitive inhibitors and autoradiographic studies could give an answer to these questions.

Two other kinetic considerations from this study deserve further discussion: In the first place there does not seem to be an enterohepatic recirculation of butylscopolamine, methylatropine and propantheline, since after intravenous injection of these compounds in patients with and without T-tube drainage, an equal amount of administered radioactivity is excreted in the urine. Cetiedil or its metabolite(s) may be subjected to an enterohepatic recirculation

since after intravenous injection in patients without a T-drain a higher percentage of the administered radioactivity is excreted in urine than in patients with a T-drain. It could be calculated that the big amount of radioactivity in faeces after oral and rectal administration of butylscopolamine, methylatropine and propantheline has not entered the general circulation and therefore a possible enterohepatic recirculation is negligible. An enterohepatic recirculation after oral and rectal administration of cetiedil may exist. In the second place, it can be calculated that after intravenous injection of butylscopolamine the maximal level of radioactivity in bile approximates 160 times the plasmalevel that would have given a maximal inhibition of saliva secretion if present in plasma. If one accepts that after oral administration approximately 1% of the i.v. maximal plasmalevel will be reached and that the bile concentration will follow proportionally, the latter concentration might affect the biliary tract musculature if the epithelial lining were permeable for butylscopolamine. Our experiments that were invented to demonstrate or to deny such a possibility failed, but they led us stepwise to a conclusion of equal importance, namely that at least butylscopolamine may exert a direct antispasmodic action on the human ureter, that is not mediated by an anticholinergic mechanism. This is in contrast with atropine and therefore important for the choice of anticholinergic "support" of opiate medication in cases of renal calculus. This work is presented in chapter 6.

As a final conclusion we may say that the search for a better understanding of the relationship between dose, plasmalevel, effect and intrinsic potency of 4 anticholinergic drugs yielded a varying, partly unexpected, but nevertheless interesting information. Methylatropine seemed to do what one might expect: a rather poor absorption, some metabolism and effects - probably due to the parent drug - that are in accordance with the intrinsic potency of the compound. Propantheline was subjected to considerable metabolic degradation, especially after oral administration. Still, not the splitting products, as one could have speculated, are responsible for the effects, but the small proportion of unchanged drug that will reach the general circulation. A pharmacodynamic behaviour that fits well with the very high intrinsic potency of the drug. The tertiary amine cetiedil will certainly not reach the general circulation in an un-

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changed form after either oral or rectal administration. Still, an obvious anticholinergic effect is observed; one can conclude that, in contrast with propantheline, an active metabolite must be involved here. Finally, butylscopolamine: hardly any effect after enteral administration. Wether this is true for the gut is not clear: the large volume of distribution is compatible with local accumulation especially in the intestines. And as far as the effect on other smooth musculature, i.e. the ureter, is concerned: the effect does not seem to depend on the anticholinergic potency at all, but rather, on a non-specific, so-called musculotropic mechanism. This is not shared by atropine and, in clinical practice, it will probably be of no importance for methylatropine and propantheline.

Hence, though cholinergic transmission is a relatively well understood mechanism and the antagonism by anticholinergics as well, the work presented in this thesis indicates that in fact a great discrepancy between the simple mechanism and clinical practice may be found that is due to a great variability in the dose - plasmalevel - effect - intrinsic potency relationships of the drugs that are in use.

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